IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants: Linda G. Cima, Edward W. Merrill, and Philip R. Kuhl

Serial No.: 08/398,555 Group Art Unit: 1811

Filed: March 3, 1995 Examiner: Jeffrey E. Russel

For: *CELL GROWTH SUBSTRATES WITH TETHERED CELL GROWTH EFFECTOR MOLECULES*

Assistant Commissioner
for Patents
Washington, D.C. 20231

PETITION FOR ENTRY OF AMENDMENT

Sir:

Pursuant to 37 C.F.R. §1.181, Applicants hereby petition from the refusal of the Examiner to enter the Amendment filed September 4, 1997 in the present application. This Petition includes a statement of the facts involved, the points to be reviewed, and the action requested. This petition is timely, being filed within two months after refusal of entry of the Amendment by the Examiner in an Advisory Action mailed September 16, 1997. A Notice of Appeal is being filed with this Petition. A Petition for Extension of Time for One Month, to extend the time for response up to and including October 14, 1997, along with the fee for a small entity is attached. It is believed that no fee is required with this submission. However, should any additional fee be required, the Commissioner is hereby authorized to charge the fee to Deposit Account No. 01-2507. To facilitate this process, a duplicate of this Petition is enclosed.

Statement Of Facts

The Claimed Invention

The claimed invention includes compositions and methods for stimulating the growth of eukaryotic cells. A substrate has tethered thereto an effective concentration of one or more growth effector molecules to enhance the rate of target cell growth over the rate of target cell growth with soluble growth effector molecules and growth effector molecules merely adsorbed to a substrate, without internalization of the molecules. The tethers are made from biocompatible, synthetic, water soluble polymers. As added by the proposed amendments, the tethers are branched so as to be able to covalently link more than one growth effector molecule. Dependent claims specify the materials of the substrate and the tethers, specify the growth effector molecules, specify the length of the tethers, and provide modifications of the method.

The Amendment Of September 4, 1997

Claims 1-6, 8-22, and 24-32 would be pending upon entry of the Amendment. Amendments to claims 1, 5, 6, 8, 13, 21, 22, 24, 31, and 32 and cancellation of claims 7 and 23 is proposed. A copy of all pending claims as they would be amended upon entry of the Amendment is attached to this Petition in an Appendix.

One proposed amendment to the claims is to more clearly define the tethers as branched so as to covalently link more than one growth effector molecule. Another proposed

amendment is to define the tethers as water soluble. A third amendment is to clarify that the rate of target cell growth is enhanced over the rate of target cell growth with soluble growth effector molecules and growth effector molecules adsorbed to a substrate. Other proposed amendments clarify that the polymer of claims 4, 5, 6, 21, and 22 is the substrate polymer, correct the dependency of claim 24, and more clearly delineate the Markush groups in claims 6 and 8.

The proposed amendments clarify the claimed subject matter and more clearly distinguish the claimed subject matter from the cited prior art. The amendments were made in response to rejections initially made in the Office Action of April 14, 1997, apparently by a different Examiner, who finally rejected the claims. In particular, §112 rejections were made for the first time and §§102 and 103 rejections were made based upon prior art cited for the first time in the Office Action mailed April 14, 1997.

The Advisory Action Of September 16, 1997

The Advisory Action denies entry of the Amendment of September 4, 1997 and maintains the final rejection of the claims. In particular, it is stated that the Amendment is denied entry because the addition of limitations requiring branched tethers able to covalently link more than one growth effector molecule raises new issues that would require further consideration and/or search. As evidence, the Examiner points to U.S. Patent No. 5,414,075 to Swan which allegedly discloses branched spacers through which are attached target molecules.

The Advisory Action states that the other amendments would have been entered had they been submitted separately and that their entry would overcome the rejections set forth in paragraphs 2 and 3 of the final Office Action of April 14, 1997. Those rejections were made under §112, second and fourth paragraphs. If the Amendment of September 4, 1997 is entered, the sole remaining issues for Appeal will be the prior art rejections under §§102 and 103. This would narrow issues on appeal.

Points To Be Reviewed

The point to be reviewed is whether the Amendment of September 4, 1997 should be entered. More specifically, the point to be reviewed is whether the amendment to the claims to define the tethers as branched so as to be able to covalently bind more than one growth effector molecules raises new issues requiring further consideration and/or search.

Action Requested

Applicants request that the Amendment filed September 4, 1997 be entered. If the amendment is entered, Applicants request that the rejections under §§102 and 103 be reconsidered by the Examiner.

Argument

Support For The Proposed Amendments At Issue Is Found In The Specification

Support for the aspect of the tethers being branched and being able to covalently link more than one growth effector molecule is explicitly found in the specification at page 4, lines 16-18, where it is disclosed that "In a preferred embodiment, multiple growth factors and/or matrix materials are attached to a single core molecule, such as a star polymer." Star polymers are further discussed and defined at page 7, lines 3-20.

The Claims As Filed Encompass The Embodiments Defined By The Claims As Proposed To Be Amended

The claims as originally filed defined the tethers as "biocompatible . . . wherein one end of each tether is covalently linked to the substrate and each growth effector molecule is covalently linked to a distal end of a tether." Therefore, the claims as filed encompassed both branched and linear tethers.

The Examiner's Original Search Revealed Art Disclosing Branched Polymers

The original search conducted by the Examiner revealed art that is drawn directly to branched, star polymers. See U. S. Patent No. 5,171,264 to Merrill. It is unclear to Applicants why a new search is needed when the original search identified art disclosing star polymers. Moreover, the Examiner stated in the first Office Action that "Merrill discloses star polymers ... which can have one arm covalently linked to a substrate . . . and another

arm covalently linked to a bioactive molecule." See the Office Action of August 19, 1996 at page 7, lines 11-16. Therefore, the explicit recitation of the limitation at this time does not require further consideration or a new search.

The Amendments Conform to 37 C.F.R. §1.116

The proposed amendments are necessary because they better define the claimed compositions and methods over the prior art. The proposed amendments do not raise issues of new matter, as noted by the Examiner in the Examiner's Interview Summary Record of September 4, 1997. The proposed amendments place the application in better form for appeal because the number of issues for appeal have been materially reduced. If the amendment is entered, there will be no §112 issues remaining. The proposed amendments do not present additional claims and, in fact, reduce the number of claims. Further, as discussed above, the proposed amendments do not raise new issues that require further consideration and/or search.

CONCLUSION

Entry of the Amendment for purposes of appeal is therefore earnestly solicited.

Respectfully submitted,

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CERTIFICATE OF MAILING UNDER 37 CFR §1.8a

I hereby certify that this Petition, along with any paper referred to as being attached or enclosed, is being deposited with the United States Postal Service on the date shown below with sufficient postage as first-class mail in an envelope addressed to the Assistant Commissioner of Patents, Washington, D.C. 20231.

Eva Mukasa

Date: September 24, 1997

APPENDIX: Claims Pending upon Entry of Amendment

1. (twice amended) A composition for stimulating the growth of eukaryotic cells comprising

a biocompatible solid substrate,

biocompatible synthetic branched water soluble polymeric tethers, and

growth effector molecules,

wherein one end of each tether is covalently linked to the substrate and each growth effector molecule is covalently linked to a distal end of a tether so that the growth effector molecule cannot be internalized by cells attached to the substrate, each tether is able to covalently link more than one growth effector molecule, and

the growth effector molecules are attached to the substrate in a concentration effective to enhance the rate of target cell growth over the rate of target cell growth with soluble growth effector molecules and growth effector molecules adsorbed to a substrate without internalization of the molecules.

2. The composition of claim 1 wherein the form of the biocompatible substrate is selected from the group consisting of netting, individual and woven fibers, sponge and shaped polymers.

3. The composition of claim 2 wherein the shape of the shaped polymer is selected from the group consisting of dishes, bottles, solid particles, hollow particles, and polymers shaped to match a desired tissue shape.

4. The composition of claim 1 wherein the biocompatible substrate is selected from the group consisting of glasses, metals and biocompatible polymers.

5. (twice amended) The composition of claim 4 wherein the substrate polymer is selected from the group consisting of synthetic polymers and natural polymers.

6. (twice amended) The composition of claim 5 wherein the substrate polymer is selected from the group consisting of proteins, polysaccharides, polyesters, polycapralactone, polyhydroxybutyrate, polyanhydrides, polyphosphazenes, polyorthoesters, polyurethanes, and combinations thereof.

8. (amended) The composition of claim 1 wherein the tether is selected from the group consisting of polyethylene oxide and carboxymethylcellulose.

9. The composition of claim 1 wherein the growth effector molecules are selected from the group consisting of epidermal growth factor, platelet-derived growth factor, transforming growth factor, hepatocyte growth factor, heparin binding factor, insulin-like growth factor I or II, fibroblast growth factor, erythropoietin, nerve growth factor, bone morphogenic proteins, muscle morphogenic proteins, extracellular matrix molecules, and combinations thereof.

10. The composition of claim 1 wherein the tether has a backbone length between 5 and 50,000 atoms.

11. The composition of claim 10 wherein the tether has a backbone length between 100 and 50,000 atoms.

12. The composition of claim 10 wherein the tether has a backbone length between 5 and 500 atoms.

13. (twice amended) A method for growing eukaryotic cells comprising

(a) bringing into contact the cells and a composition comprising

a biocompatible solid substrate,

biocompatible branched water soluble polymeric tethers, and

growth effector molecules,

wherein one end of each tether is covalently linked to the substrate,

each tether is able to covalently link more than one growth effector molecule,

each growth effector molecule is covalently linked to a distal end of a tether so that the growth effector molecule cannot be internalized by cells attached to the substrate, and

the growth effector molecules are attached to the substrate in a concentration effective to enhance the rate of target cell growth over the rate of target cell growth with soluble growth effector molecules and growth effector molecules adsorbed to a substrate, without internalization of the molecules; and

(b) maintaining the contacting cells and composition under conditions and for a time sufficient to cause the cells to grow.

14. The method of claim 13 wherein the step of bringing into contact comprises administering the composition to a patient in need of cell growth.

15. The method of claim 14 wherein the composition is administered by injection, infusion, or implantation.

16. The method of claim 15 wherein the composition is administered by implantation of the composition and wherein the substrate is shaped to match a desired tissue shape.

17. The method of claim 16 wherein the substrate is biodegradable.

18. The method of claim 13 wherein the form of the biocompatible substrate is selected from the group consisting of netting, individual and woven fibers, sponges and shaped polymers.

19. The method of claim 18 wherein the shape of the shaped polymer is selected from the group consisting of dishes, bottles, solid particles, hollow particles, and polymers shaped to match a desired tissue shape.

20. The method of claim 13 wherein the biocompatible substrate is selected from the group consisting of glasses and biocompatible polymers.

21. (amended) The method of claim 20 wherein the substrate polymer is selected from the group consisting of synthetic polymers and natural polymers.

22. (amended) The method of claim 21 wherein the substrate polymer is selected from the group consisting of polylactic acid, polyglycolic acid, polyanhydrides, polyorthoesters, collagen, glycosaminoglycans, polyamino acids, and combinations thereof.

24. (amended) The method of claim 13 wherein the tether is selected from the group consisting of polyethylene oxide, carboxymethylcellulose, and starch.

25. The method of claim 13 wherein the growth effector molecules are selected from the group consisting of epidermal growth factor, platelet-derived growth factor, transforming growth factor, hepatocyte growth factor, heparin binding factor, insulin-like growth factor I or II, fibroblast growth factor, erythropoietin, nerve growth factor, bone morphogenic proteins, muscle morphogenic proteins, extracellular matrix molecules, and combinations thereof.

26. The method of claim 13 wherein the tether has a backbone length between 5 and 50,000 atoms.

27. The method of claim 26 wherein the tether has a backbone length between 100 and 50,000 atoms.

28. The method of claim 13 wherein the tether has a backbone length between 5 and 500 atoms.

29. The method of claim 13 wherein the cells are selected from the group consisting of parenchymal cells and stem cells.

30. The method of claim 29 wherein the cells are hepatocytes.

31. (twice amended) A cell culture comprising
a biocompatible solid substrate,
biocompatible branched water soluble polymeric tethers,
growth effector molecules, and
growing cells,

wherein one end of each tether is covalently linked to the substrate, each tether is able to covalently link more than one growth effector molecule,

each growth effector molecule is covalently linked to a distal end of a tether so that the growth effector molecule cannot be internalized by cells attached to the substrate, the growth effector molecules are attached to the substrate in a concentration effective to enhance the rate of target cell growth over the rate of target cell growth with soluble growth effector molecules and growth effector molecules adsorbed to a substrate, without internalization of the molecules, and wherein the growing cells are bound to the growth effector molecules.

32. (twice amended) A method of testing a compound for an effect on tissue comprising

(a) bringing into contact the compound to be tested and a composition comprising
a biocompatible solid substrate,
biocompatible branched water soluble polymeric tethers,
growth effector molecules, and
growing cells,

wherein one end of each tether is covalently linked to the substrate, each tether is able to covalently link more than one growth effector molecule,

each growth effector molecule is covalently linked to a distal end of a tether so that the growth effector molecule cannot be internalized by cells attached to the substrate,

the growth effector molecules are attached to the substrate in a concentration effective to enhance the rate of target cell growth over the rate of target cell growth with soluble growth effector molecules and growth effector molecules adsorbed to a substrate, without internalization of the molecules, and wherein the growing cells are bound to the growth effector molecules;

(b) incubating the compound and the composition under conditions promoting cell growth; and

(c) observing the cells for any effect not observed in cells not brought into contact with the composition.